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CASE-CONTROL STUDY OF CHILDHOOD LEUKEMIA AND LYMPHOMA NEAR THE SELLAFIELD NUCLEAR PLANT

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This study examined excess incidence of childhood leukemia and lymphoma in children who lived near the Sellafield nuclear plant. The authors sought to determine if this excess was associated with established risk factors or with factors related to the plant or proximity to it.

A case-control study included 52 cases of leukemia, 22 cases of non-Hodgkin's lymphoma, and 23 cases of Hodgkin's disease. Cases were under the age of 25 y, had been born in the area, and had been diagnosed in the area from 1950 to 1985. A total of 1 001 controls taken from the same birth registers in which the cases were entered were selected. Data on antenatal abdominal x-rays, viral infections, behavioral factors, residential and occupational histories (including radiation dosimetry, etc.) were obtained from (a) medical records, (b) questionnaires to parents, and (c) linkage to Sellafield employment records.

To date, analysis has revealed that data quality is good. Concordance from duplicate sources, where available, is reasonably high with no indications of bias between cases and controls. Major analysis of the geographical distributions and potential explanations in terms of radiation exposure from the plant (e.g., ingestion of seafood, playing on the beaches, or parental employment) is currently underway and will be completed in the spring.

LUNG CANCER RISKS OF RESIDENTIAL RADON EXPOSURE IN NEW JERSEY

JB Schoenberg, JB Klotz, HB Wilcox

Government and private sector activities to reduce residential radon exposure are primarily based on extrapolation of data on lung cancer risk from the underground mine to the home setting. In 1985, the New Jersey Department of Health extended a previously conducted, statewide, population-based case control study of lung cancer in women to include radon measurements in former homes of the subjects. The principal objective was to determine if a lung cancer risk consistent with the mining study would be observed in this population.

The study extension collected year-long living-area radon exposure data in one residence for each of 433 histologically confirmed lung cancer cases and 402 controls. Previously, data on smoking, occupation, and diet had been collected for 994 cases and 995 controls. The criterion for inclusion was occupancy of a single residence for at least 10 y during the 10 to 30-y period that preceded ascertainment of cases or selection of controls.

Despite the few subjects who had high exposures and the gaps in exposure histories, a significant trend ($p = .04$) for lung cancer risk and exposure intensity was found, as was a slightly weaker trend ($p = .09$) for cumulative exposure. Further, the calculated relative risk coefficient per cumulative exposure unit (3.4% per WLM) was generally consistent with those of the underground miner studies. There was an inconsistent pattern of radon interaction with smoking.

Although the findings must be viewed cautiously, they support the current public health policy of assuming that the unit risks of radon documented for male miners also apply to lower exposures in the general population.

RADIATION AND MORTALITY AMONG WORKERS AT THE OAK RIDGE NATIONAL LABORATORY: FOLLOW-UP THROUGH 1984

S Wing, CM Shy, J Watson, S Wolf, J Wood, D Cragle, E Frome

A cohort of white male workers (N = 8 318) employed at a Department of Energy research and development facility for more than 30 d between 1943 and 1972 was followed through 1984. There were 1 524 deaths and a loss to follow up of 8%. Estimates of exposure to penetrating external radiation were available from individual badges for 95% of working years; doses were estimated from nearby doses in years for which there were no data. Cumulative external dose was less than 10 mSv for 6 042 workers and greater than 50 mSv for 638 workers. A total of 3 740 workers were monitored for internal radiation exposure at some time during their employment at the plant.

The standardized mortality ratio (SMR) was 0.7 for all causes and 0.8 for all cancers. Leukemia SMRs were 1.6 (28 observed) for the total group and 2.2 (16 observed) among the subgroup that also had been monitored for internal exposure. No other cancer SMRs were significantly elevated. Excess leukemia mortality occurred after 1960 among workers hired prior to 1960. Standardized rate ratios (SRRs) using multiple-cause-of-death data, adjusted for age and calendar year, were calculated with the total population as the referent. Leukemia SRRs in the < 10, 10 to 50, and 50+ mSv groups were 0.8 (15 deaths), 1.6 (13 deaths), and 0.6 (2 deaths), respectively, with a 2 y exposure lag. Leukemia SRRs, excluding chronic lymphocytic leukemia, showed a similar pattern. Work in progress estimating dose-response relationships for leukemia and other cancer sites based on time-dependent lifetable regression models, adjusting for active worker status and other co-variates, will be presented.

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EFFECTS ON EARLY CHILDHOOD DEVELOPMENT OF PRENATAL EXPOSURE TO METHYLMERCURY

T Kjellström

A follow-up study of the developmental and psychological effects of prenatal exposure to methylmercury via fish was conducted in a group of New Zealand children whose mothers had a high fish consumption during pregnancy. Preliminary studies showed that fish with elevated mercury levels were sold in Auckland shops, and people who consumed substantial amounts of fish could reach intakes of mercury 3–4 times the WHO/FAO provisional tolerable weekly intake.

Mercury analysis of maternal hair identified 74 children with average prenatal exposure above 6 mg Hg/kg hair. These children were matched with three reference groups with lower exposures, and their performances in scholastic, psychological, and behavioral tests were compared.

The main findings were than (1) the "normal" results of the psychological test variables were influenced by the child's ethnic background and social class, (2) there is an apparent consistent association between high prenatal methylmercury exposure and decreased performance in the tests, (3) methylmercury exposure contributes only a small part of the variations in test results, and (4) an average hair mercury level during pregnancy of 13–15 mg Hg/kg hair was associated with the decreased test performance.

For the children who were tested both at age 4 y and age 6 y, there was a tendency for an association between the results of the Denver test at age 4 y and the Wechsler IQ at age 6 y. This indicates that the effects on the child's development and mental functions may be enduring.

LOOKING FOR TROUBLE: A CLINICAL PERSPECTIVE FOR FOCUS IN ENVIRONMENTAL EPIDEMIOLOGY IN THE 1990s

BW Case

Much has been written about the need for better exposure assessment, disease definition, statistical prowess, and "biologic rationale" in the conduct of environmental epidemiology. Not as much thought has been given to temporal trends in each of these very separate disciplines and their separate and combined effects on our knowledge of the environmentally diseased man, woman or child. Historically, epidemiology took the form of the classic detective story: the body on the floor (or in the hospital bed); the clue (exposure surrogate? disease? biomarker?) leading to the criminal (common source) who was quickly dispatched (prevention!). Unfortunately, the clues in our science have overwhelmed the crimes: in the process, we may lose our focus on the patient. Instrumentation and detection limits have made exposure assessment and its biologic surrogates far more accurate than exposure "reconstruction" pretends to be. Our understanding of disease (both definition and cause) have improved apace, yet we continue to rely on outmoded (ICD) codes and imperfect, nonspecific, and often biologically questionable "biomarkers." Most particularly, statistical analysis (and "risk assessment") have advanced to the point where a data set, if large enough and having enough covariates, may threaten to engulf the most intrepid investigator for years in what should have been a test of one null hypothesis. Even when this temptation is avoided, the effects of heterogeneity (genetic or otherwise) are dealt with inadequately, and potential confounders are unknown, much less accounted for. Biologic rationale is usually given token attention; besides, it can always be found before or after the fact (study) if we look long and hard enough. The result: a confused public, a welter of litigation, a plethora of artificially created problems, and exponentially increasing choices for *what to study* in an era of decreasing real funding. In this presentation, the following devil's advocacies are made. (1) Environmental epidemiology is a branch of clinical medicine. (2) As such, it should "do no harm," and it has the potential to do harm, e.g., in one location *preventing* fluoridation of water, in many instances undermining confidence in adequate nutrition and other public health measures, and even in one instance threatening lives on a grand scale in underdeveloped countries. (3) Accurate measurement is no substitute for accurate clinical thinking as to what, why, and whom to measure. (4) The *sine qua non* of choice must be not fundability, fashion, or flow charts: it must be clinical relevance. The importance of lead, cigarette smoke, and "clean air" will be used as examples, with converse examples being (non-amphibole) asbestos, some manmade mineral fibers, and selected environmental chemical exposures.

CLINICAL MANIFESTATIONS OF EOSINOPHILIA-MYALGIA SYNDROME

K Waller, D Hatch, T Saunders, L Goldman

Eosinophilia-myalgia syndrome (EMS) is a recently described illness associated with the use of supplemental L-tryptophan (L-T). The illness is characterized by unexplained peripheral eosinophilia (> 1 000 cells/mm³) and disabling myalgia, but the full range of clinical manifestations of EMS has not yet been described. As of February 8, 1990, 236 EMS cases have been reported to the California Department of Health Services (CDHS); 4 of these patients have died. This report summarizes clinical features and laboratory findings in 118 EMS patients for whom completed case report forms were available. The majority of cases were white middle-aged females; 87% of patients became ill during or after July 1989. Twenty-nine percent had been hospitalized. Symptoms reported by more than half of the patients included arthralgia (69%), dyspnea or cough (64%), rash (64%), and edema (51%). Pulmonary infiltrates were found in 16% of patients who received chest radiographs. Neuropathy had been diagnosed in 14% of patients; 3 have progressed to quadraparesis. Cardiac complications were reported in 6 patients. All patients reported use of L-T supplements prior to onset of illness; there was no clear relationship between dose or length of L-T use and severity of symptoms. EMS is a multisystemic illness that may have serious sequelae in some patients.

IMMUNOHISTOLOGICAL STUDY OF AFLATOXIN B_1, HEPATITIS B VIRUS AND HEPATOCELLULAR CARCINOMA

YJ Zhang, CS Lee, CY Yang, SN Lu, LL Hsieh, SL You, WL Wang, CJ Chen, RM Santella

The extraordinarily high hepatocellular carcinoma (HCC) mortality in Taiwan has been attributed to chronic hepatitis B virus (HBV) infection. However, epidemiologic studies have also suggested the importance of other environmental factors in the development of HCC. This immunohistological study examined the association of HCC with aflatoxins and HBV. Surgically removed and needle-biopsied HCC tissues and adjacent normal liver tissues were obtained from HCC patients in Taiwan and United States. An immunofluorescence method in which antibodies generated against the imidazole ring-opened form of major N7 guanine adducts of aflatoxin B_1 was used for the detection of aflatoxin-DNA adducts in these tissues. A peroxidase-antiperoxidase method that uses commercial kits (Biogenex Laboratories, Dublin, California) was employed for the detection of HBV surface antigen (HBsAg) in frozen tissue sections. Approximately 10% of HCC tissues from patients in Taiwan had detectable aflatoxin B_1 adducts, but the adduct was not detected in any HCC tissue obtained from patients in the United States. The HBsAg was detected in tumor tissues of 44.4% HCC patients and in adjacent normal tissues of 71.4% HCC patients from Taiwan, but none of the tumor or adjacent normal tissues from HCC patients in the United States was positive for HBsAg. Albumin adducts of aflatoxin B_1 in HCC patients and matched controls are also being carried out. The relative importance of these findings will be discussed.

AN EPIDEMIOLOGICAL STUDY OF LUNG CANCER IN XUAN WEI COUNTY, CHINA: CURRENT PROGRESS (I)

X He, W Chen, Z Liu, RS Chapman

In Xuan Wei County, Yunnan Province, lung cancer mortality rates are among China's highest in males and females. Previous studies have shown a strong association of lung cancer mortality with air pollution from "smoking" coal combustion. In the present quantitative risk assessment of indoor air pollution, this study shows a strong, obvious, on-site exposure-response relationship between Benzo(a)pyrene concentration in indoor air and lung cancer mortality. The results of this study strongly suggest the hypothesis that the indoor air pollution is the main risk factor for inducing lung cancer in Xuan Wei County. In the present case-control study, 100 newly diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence, which provided matching with respect to fuel use. Data from males and females were analyzed by conditional logistic regression. The results show that the presence of lung cancer in females who do not smoke is statistically significantly associated (at alpha = .05) with chronic bronchitis and family history of lung cancer. The results also suggest an association of lung cancer with duration of cooking food but not with passive smoking. The presence of lung cancer in males is

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associated with smoking, chronic bronchitis, family history of lung cancer, and personal history of cooking food. Effects of smoking and bronchitis in males are independent. Our studies suggest that lung cancer in Xuan Wei may occur through more than one mechanism of production. An etiologic study of lung cancer in nonsmokers is now in progress in Xuan Wei County, China.

EFFECTS OF OZONE ON LUNG FUNCTION IN CHILDREN LIVING IN THE NETHERLANDS

B Brunekreef, E Lebert, G Hoek, A van Kessel

In the Netherlands, a study is being conducted to investigate the temporal relationship between air pollution and lung function in school children. Several pollutants are measured continuously, among which are sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), airborne particulate (PM_{10}), and acid aerosols. Lung function is measured at the schools (mostly during the morning hours) at intervals from 1–3 wk, with more frequent measurements when pollutant levels are (expected to be) high.

During May and June 1989, relatively high levels of O_3 were observed in the Netherlands. On several days, 1-h maximum levels were between 200 and 240 $\mu g/m^3$, and 8-h maximum levels were between 160 and 200 $\mu g/m^3$.

About 500 children were studied during this period, and for each child a regression analysis was used to relate lung function to various measures of O_3 exposure. All analyses were linearly adjusted for the day of the year to correct for temporal trends in the data resulting from growth, learning effects, or motivational effects.

Only for PEF was the median of the estimated regression coefficients found to be significantly different from zero, with an estimated decrease of PEF of 5% at a 1-h maximum O_3 level (as measured on the day preceding the lung function tests) of 200 $\mu g/m^3$. FVC, $FEV_{1.0}$, and MMEF were not associated with exposure to O_3.

ARSENIC AND CADMIUM EXPOSURE IN CHILDREN LIVING NEAR TO BOTH ZINC AND COPPER SMELTERS

F Diaz-Barriga, MA Santos, L Batres, JJ Mejia, G Galvan, L Yanez, R Villalobos, M Zanatta, JL Medina, L Carrizales, H Hernandez, E Llamas

Exposure to both arsenic and cadmium is a common occurrence in San Luis Potosi City, Mexico. Two of the biggest smelters in Mexico are close to the City. One smelter produces approximately 8 500 tons of arsenic trioxide annually, and the other smelter produces about 700 tons of cadmium annually.

In this study, arsenic and cadmium levels were determined simultaneously in multiple environmental media and also from children's (3–6 y of age) urine. Two urban and one rural zone, respectively, were included: (1) Morales, which was within 2 km of the smelters; (2) Graciano, located 7 km from the smelters; and (3) Mexq, a rural community distanced 25 km from the smelters. Environmental media that was sampled included air, soil, household dust, and tap water.

Results of this investigation showed increased environmental cadmium levels close to the smelters for only soil, dust and, in some samples, air. Cadmium levels in urine samples collected from children who lived in the three areas did not differ. There were significantly higher levels of arsenic in tap water from the urban zones. The same relationship held for arsenic levels in soil and dust. (The air samples are being processed; therefore, results are not yet available.) Finally, increased systematic absorption of arsenic, as evidenced by urine arsenic levels, was clearly noted in children who lived near the smelters. The results obtained from questionnaires that were completed by mothers and teachers showed significant differences in intellectual performance and incidence of respiratory disease (confirmed by clinical examination) between children residing in urban and rural areas.

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CONSEQUENCES OF AGENT ORANGE ON HEALTH: THE INSERM STUDY IN VIETNAM

INSERM North-South Network for Environmental Epidemiology in Vietnam*

The INSERM North-South Network* for Environmental Epidemiology in Vietnam is presently conducting three studies regarding exposure to herbicides during war and (a) non-Hodgkin's lymphoma, (b) primary carcinoma of the liver, and (c) molar pregnancy and choriocarcinoma. The three case-control studies consist of 100 cases and 100 controls for each pathology, matched by sex, age, and residency. Known confounders are assessed, e.g., (1) professional and other environmental exposures (all studies), (2) HBV infection and aflatoxins (study b), (3) reproductive history and nutritional status (study c). Exposure is assessed by a blind interview on past residency and war affectations, correlated with the US HERBS TAPE, and blood sampling for future measurements of 2,3,7,8-tetrachlorodibenzodioxin. To date, a French team has spent a total of 6 mo in Vietnam.

The feasibility of the three case-control studies will be discussed at the meeting. Epidemiologic investigations of dioxin exposure in Vietnam are actually feasible and cost-effective.

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A FOLLOW-UP STUDY OF THE COMMUNITY NEAR THE McCOLL WASTE DISPOSAL SITE

JA Lipscomb, L Goldman, K Satin, D Smith, W Vance, R Neutra

In this study, the effect of interim clean-up measures on the current health of a community was investigated. We conducted a follow-up survey of 193 residents who lived near the McColl waste disposal site and near a nearby comparison area. Results from this survey were compared with results from a similar survey conducted 7 y earlier. Odors were detected at least once per week by 32.7% of "highly exposed" respondents in 1988 compared with 68.5% in 1981. However, prevalence odds ratios (PORs) that compared reporting of symptoms by residents in these two areas were greater than that of the 1981 survey for 89% of the symptoms. The PORs that compared reporting of symptoms between these two areas were greater than 2.0 for 64% of symptoms assessed in the current survey. Symptoms reported in excess did not represent a single organ or system or suggest a mechanism of response. The PORs that compared respondents who were very worried about the environment and those reporting no worry were greater than 2.0 for 86% of symptoms. These findings and environmental data from the area suggest that living in the McColl area and being very worried about the environment, rather than a toxicologic effect of chemicals from the site, explain the excess reported symptoms observed in this follow-up study.

SYMPTOM PREVALENCE AND ODOR-WORRY INTERACTION NEAR HAZARDOUS WASTE SITES

D Shusterman, J Lipscomb, R Neutra, K Satin

Retrospective symptom prevalence data collected from more than 2 000 adult respondents who lived near three different hazardous waste sites were analyzed with respect to both self-reported "environmental worry" and frequency of smelling environmental—particularly petrochemical—odors. Significant positive relationships were observed between the prevalence of several symptoms (e.g., headache, nausea, eye and throat irritation) and both frequency of odor perception and degree of worry. Headache, for example, showed a prevalence odds ratio of 5.0 for respondents who reported smelling environmental odors frequently vs. those smelling no such odors, and 10.8 for those who described themselves as "very worried" vs. "not worried" about environmental conditions in their neighborhood. Elimination of respondents who ascribed their environmental worry to illness in themselves or in family members did not materially affect the strength of the observed associations (corrected prevalence odds ratios 5.6 and 11.1, respectively). In addition to their independent effects, odor perception and environmental worry exhibited positive interaction as determinants of symptom prevalence, as evidenced by a prevalence odds ratio of 38.1 for headache among the high-worry/frequent-odor group vs. the no-worry/no-odor group. In comparison for neighborhoods with no nearby waste sites, environmental worry was also associated with symptom occurrence. Potential explanations for these observations are presented, including the possibility that odors serve as a sensory cue for the manifestation of stress-related illness among individuals who are concerned about the quality of their neighborhood environment.

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